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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,184	COWSERT, LEX M.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 1999*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of: .

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-15-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,962,672 (US'672). Although the conflicting claims are not identical, they are not patentably distinct from each other because

(a) Claims 1-11 of the instant application are drawn to antisense compounds of 8 to 30 "nucleotides" in length targeted to a nucleic acid molecule encoding human RhoB, wherein said antisense compound inhibits the expression of human RhoB; antisense compounds of claim 1 which is an antisense oligonucleotide; the antisense compounds of the specific SEQ ID NO: set forth in claims 3-4; the antisense oligonucleotide of claim 2 which comprises at least one modified internucleoside linkage, wherein said modified linkage is a phosphorothioate linkage; the antisense compound of claim 2 which comprises a modified sugar, wherein said modified sugar is a 2'-O-methoxyehtyl sugar moiety; the antisense compound of claim 2 which comprises

at least one modified nucleobase, wherein the modified nucleobase is 5-methycytosine; and wherein the oligonucleotide of claim 1 is a chimeric oligonucleotide.

Claims 1-11 of US'672 differ from instant claims 1-11 to the extent that they recite antisense compounds of 8 to 30 "nucleobases" in length targeted to SEQ ID NO: 1, and the instant claims recite antisense compounds of 8 to 30 "nucleotides" in length targeted to nucleic acid encoding human RhoB. Additionally, instant claims 3-4 also differ from claims 3-4 of US'672 since they do not recite wherein the antisense compound comprises at least an 8-nucleobase portion of the specific sequences recited in these claims according to "SEQ ID NO:."

The disclosure of US'672 supports wherein the antisense compounds of the instant invention are "8 to 30 "nucleotides" in length, and wherein the antisense compound comprises at least an 8-nucleobase portion of the sequences recited in claims 3-4. For example, col. 5, lines 25-29 recites, "[t]he antisense compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases. Particularly preferred are antisense oligonucleotides comprising from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides)." It is clear that since antisense compounds of 8 to 30 nucleobases in length are the preferred lengths of the antisense compounds of US'672, antisense compounds of the present invention would encompass those antisense compounds comprising an at least 8 nucleobase portion of the specific antisense oligonucleotides disclosed in the US'672 and in the specification as filed (see tables 1-2). Moreover, in regards the "nucleotide" limitation recited in the instant claims, the disclosure of US'672 (col. 5, lines 27-35) recites "[P]articularly preferred are antisense oligonucleotides comprising from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleosides). As is known in the art, a nucleoside is a base-sugar combination.

The base portion of the nucleoside is normally a heterocyclic base. The two most common classes of such heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside." It is clear from the disclosure of US'672 that a nucleotide is a specifically disclosed species of the genus of nucleobase moieties encompassed by the invention of US'672. Additionally, in regards to the "SEQ ID NO: 1" recited in the issued claims, the instant specification only discloses one human RhoB nucleic acid having a sequence in accordance to SEQ ID NO: 1, GenBank Accession No. X06820.

Instant claims 1-11 cannot be considered patentably distinct from claims 1-11 of US'672 when there are specifically recited embodiments in the disclosure of US'672 that would anticipate instant claims 1-11. Moreover, it would have been obvious to one having ordinary skill in the art to modify the antisense compounds recited in claims 1-11 of US'672 to comprise "nucleotides," to comprise and at least 8-nucleobase portion of the specific sequences disclosed in US'672, and to substitute "SEQ ID NO: 1" for the nucleic acid molecule encoding human RhoB. One of ordinary skill in the art would have been motivated to do this because these limitations are preferred alternative embodiments within the scope of issued claims 1-11 of US'672.

(b) Claim 15 recites a method of inhibiting the expression of RhoB in human cells or tissues comprising contacting said cells with the antisense compound of claim 1, wherein said antisense compound is 8 to 30 "nucleotides" in length. Instant claim 15 differs from claim 12 of U.S. Patent No. 5,962,672 to the extent that it is not limited to an *in vitro* method, and the recited method uses antisense compounds comprising "nucleotides," however issued claim 12 comprises

the use of antisense compounds comprising "nucleobases." Specifically, claim 15 of the instant application encompasses a method for inhibiting the expression of RhoB that comprises both *in vitro* and *in vivo* method of inhibiting the expression of RhoB, however the method of issued claim 12 is limited to an *in vitro* method of inhibiting the expression of RhoB. In regards to the method of instant claim 15 it is generic to the method of use recited in issued claim 12 to the extent that it encompassed both an in vitro and in vivo use, therefore to this extent instant claim 15 anticipates the limitation *in vitro* limitation recited in issued claim 12. However, in regards to the use of antisense compounds comprising "nucleotides," instant claim 15 is not generic to issued claim 12, which recites the use of antisense compounds of 8 to 30 nucleobases, see the discussion above regarding the obviousness of instant claims 1-10 over issued claims 1-10.

(c) Claims 12-14 of the instant application recite pharmaceutical compositions comprising an antisense compound or antisense oligonucleotide targeting human RhoB, and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system, and claims 1-12 of US'672 recite antisense compounds targeting human RhoB and a method of inhibiting the expression of RhoB in human cells or tissues.

The portion of the specification in US'672 that supports the recited pharmaceutical compositions include several embodiments that would anticipate claims 12-14 herein, e.g., the disclosure of US'672 clearly discloses states that compositions comprising the antisense compounds according to the present invention and a pharmaceutical carrier or diluent, and further comprising a colloidal dispersion system would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell (col. 14, lines 16-40; and col. 14, lines 65-col. 15, line 2). US'672, col. 2, lines 32-33, states that one

of the embodiments of the invention includes "pharmaceutical and other compositions comprising the antisense compounds of the invention." Additionally, col. 14, lines 16-54, recite various "pharmaceutically acceptable carriers," that are useful with the claimed invention.

Claims 12-14 cannot be considered patentably distinct over claims 1-12 of US'672 when there are specifically recited embodiments that would anticipate claims 12-14. Alternatively, it would have been obvious to one having ordinary skill in the art to modify claims 1-12 of US'672 (drawn to antisense compounds targeting RhoB and a method of inhibiting the expression of RhoB in cells or tissues) by selecting specifically disclosed embodiments that support those claims, i.e., pharmaceutical compositions comprising antisense compounds targeting RhoB, a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system. One having ordinary skill in the art would have been motivated to do this because these embodiments are disclosed as being preferred embodiments within the scope of claims 1-12 of US'672. Furthermore, one having ordinary skill in the art would have been motivated to modify claims 1-12 to encompass compositions comprising a carrier or diluent, and further comprising a colloidal dispersion system since these compositions would enhance the stability of the antisense compounds introduced into cells (see US'672, col. 14, lines 60-62) and those compounds used in the method of issued claim 12 for inhibiting the expression of RhoB in human cells or tissues.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-2, 5-11, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalcman et al., Lebowitz et al. and Chardin et al. in view of Branch (1998), and Mckay et al.

5. The instant claims are drawn to an antisense compound 8 to 30 nucleotides in length targeted to a nucleic acid molecule encoding human RhoB, wherein said antisense compound inhibits the expression of human RhoB; wherein the antisense compound comprises at least one modified internucleotide linkage; one modified sugar moiety; one modified nucleobase; and wherein the antisense compound is a chimeric oligonucleotide; a method of inhibiting the expression of RhoB in human cells or tissues with antisense compounds targeting human RhoB.

Zalcman et al. (See IDS: AE) presents the art recognized need or desire to understand and elucidate the function of RhoB. To precise the role of RhoB, Zalcman et al. suggests specifically inactivating endogenous RhoB expression by the use of antisense molecules as a dominant negative inhibitor of endogenous RhoB activity (page 1943, 3rd paragraph).

Lebowitz et al. provide evidence that the farnesylated form of RhoB is required to the malignant growth of Ras transformed cells. Furthermore, Lebowitz et al. teach that farnsesyltransferase inhibitors can be used to suppress the farnesylation of RhoB and thereby suppress Ras transformation by interfering with Rho Activity (see page 6613, 4th paragraph).

Chardin et al. describe the cloning of the human rhoB gene mRNA sequence according to GenBank Accession No. X06820, as set forth in the specification as filed on page 50, as SEQ ID NO: 1.

However, neither Zalcman et al., Lebowitz et al. nor Chardin et al. disclose antisense compounds or 8 to 30 nucleotides in length, or further comprising wherein said antisense compound inhibits the expression of human RhoB; wherein the antisense compound comprises at least one modified internucleotide linkage; one modified sugar moiety; one modified nucleobase; or wherein the antisense compound is a chimeric oligonucleotide.

Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome. However, increasing the length of the oligonucleotide beyond this minimum would likely stabilize non-specific binding to mismatch sequences (p. 47, para. 5-6).

McKay et al. (5,877,309) teach the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 2), 2'-O-methoxyethyl sugar modifications (col. 8, lines 58-60), 5-methylcytosine modified nucleobase (col. 8, line 31), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 10, lines 11-44). The modified or substituted oligonucleotides of McKay et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 6, lines 38-42). Additionally, McKay et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or

diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 23-24).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of to produce the compounds and compositions according to the present invention. One of ordinary skill in the art would have been motivated to modify the teachings of Zalcman et al., Lebowitz et al. and Chardin et al. in view of Branch (1998), and McKay et al. to make the antisense compounds 8 to 30 nucleotides in length targeting human RhoB according to the present invention. One of ordinary skill in the art would have been motivated to design antisense compounds to comprise about 17 nucleobases in length or more, because antisense compounds of about 17 nucleobases in length would enhance target site specificity for the antisense to its target mRNA (Branch). One of ordinary skill in the art would have been motivated to further modify the antisense compounds according to the present invention to comprise phosphorothioate modified internucleoside linkages, 2'-O-methoxyethyl sugar modifications, 5-methylcytosine modified nucleobases, or wherein said antisense compound is a chimeric compound, because according to McKay et al. these modifications would enhance the cellular properties of antisense compounds as compared to unmodified antisense compounds. Moreover, one of ordinary skill in the art would have been motivated to design compositions comprising the antisense compounds according to the present invention and a pharmaceutical carrier or diluent, and further comprising a colloidal dispersion system because McKay et al. teach that compositions designed according to this manner would enhance the stability of

oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

Moreover, one of ordinary skill in the art seeking methods to further elucidate the role of RhoB expression in cell proliferation, and its role in regulating the malignant growth of cells associated with Ras transformation of cells, would have been motivated to design antisense oligonucleotides targeting RhoB since Zalcman et al. clearly suggests the design of antisense molecules as dominant negative inhibitors of RhoB (see page 1943, 3rd paragraph).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 3-4, 11 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is drawn to antisense compounds of 8 to 30 nucleotides in length comprising SEQ ID NO: 10, 11, 12, 14, 15, 16, 18-21, 23-27, 29-31, 33-35, 40, 42-43, 46 and 47. This claim is vague and indefinite since claim 3 is limited to wherein the antisense compound is a maximum of 30 nucleotides in length, it is unclear how a compound of 8 to 30 nucleotides in length could comprise SEQ ID NO: 10, 11, 12, 14, 15, 16, 18-21, 23-27, 29-31, 33-35, 40, 42-43, 46 and 47.

Claim 4 is drawn to antisense compounds of 8 to 30 nucleotides in length comprising SEQ ID NO: 16, 23, 27, 33, 42 and 46. This claim is vague and indefinite since claim 3 is

limited to wherein the antisense compound is a maximum of 30 nucleotides in length, it is unclear how a compound of 8 to 30 nucleotides in length could comprise SEQ ID NO: 16, 23, 27, 33, 42, and 46.

Claim 11 recites the limitation "the oligonucleotide" in claim 1. There is insufficient antecedent basis for this limitation in the claim, because claim 1 recites an antisense compound, not an oligonucleotide.

Claim 16, and those claims dependent thereon claims 17-18, recite the phrase "said animal" at line 3. There is lack of antecedent basis for this limitation in the claim since line 1 of claim 16 recites a method of treating a "human," not an "animal," which is a broader term.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, and 5-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1-2 and 5-18 read on antisense compounds 8 to 30 nucleotides in length targeted to a nucleic acid molecule encoding human RhoB, and methods of using said antisense oligonucleotide. The specification only discloses one human RhoB nucleic acid having a sequence in accordance to SEQ ID NO: 1, GenBank Accession No. X06820. However, these claims read on a broad genus of antisense oligonucleotides targeting nucleic acid molecules encoding human RhoB, that may encompass all allelic, polymorphic, and splice variants of

human RhoB. Furthermore, neither the specification, nor the claims indicate what distinguishing attributes are shared by the members of the claimed genus of antisense oligonucleotides targeting all allelic, polymorphic, and splice variant forms of human RhoB such that one skilled in the art would readily recognize other human RhoB nucleic acids, including all variants of human RhoB. Moreover, neither the specification as filed nor the claims place any limit on the size of the target nucleic acid sequences, nor the number of substitutions, deletions, insertions and additions that may be made to the claimed target nucleic acid sequences. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between the genus members are permitted, and neither the specification nor the claims provide any guidance as to what specific changes should be made. Furthermore, since Applicant's own data set forth in Table 1 (pages 50-51 of the specification as filed) indicates that an antisense compound that is designed by simple complementary base pairing to the target is not sufficient to predict the efficacy of the compound to inhibit human RhoB expression. For example, note that multiple antisense compounds are shown as having 0% inhibitory effect on the expression of human RhoB mRNA, however others have up to 39% inhibitory effect. It is evident that the ability of an antisense compound to inhibit the expression of human RhoB expression must be determined empirically, since the ability of a compound to inhibit the expression of human RhoB can not be predicted by simple complementary base pairing. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is required. Since the disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and

because the genus is highly variant, the disclosed sequence of SEQ ID NO: 1, alone is not sufficient to describe claimed genus.

See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." The guidelines also describe *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) where the court argued that an adequate written description of a nucleic acid sequence, a protein, or an effector as claimed in the instant invention, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish

or plan for obtaining the claimed chemical invention. Accordingly, an adequate written description of a nucleic acid sequence "requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of human RhoB encoding nucleic acid molecules to describe the full scope of antisense compounds encompassed by the instant claims. Thus, applicant was not in possession of the claimed genus.

10. Claims 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of human RhoB comprising the administration of antisense compounds targeting human RhoB *in vitro*, does not reasonably provide enablement for practicing the claimed methods or using the pharmaceutical compositions comprising antisense compounds *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to pharmaceutical compositions comprising antisense compounds targeting human RhoB; methods of inhibiting the expression of human RhoB in human cells or tissues comprising contacting said cells or tissues with antisense compounds targeting human RhoB; and methods of treating a human having a disease or condition associated with RhoB comprising administering to said animal (human) a therapeutically or prophylactically effective amount of the antisense compound targeting human RhoB. The pharmaceutical compositions and methods of use recited in the instant claims require the *in vivo*

applicability of the antisense compounds of the claimed invention and the correlation between RhoB inhibition *in vivo* and the production of secondary treatment effects directly associated with conditions resultant from over expression of human RhoB. The specification as filed provides only a demonstration that only select antisense compounds are effective to inhibit human RhoB expression in cell culture, see Tables 1 and 2. However, these results cannot be used to predict the behavior of the disclosed antisense compounds *in vivo*. There is no guidance and/or instruction that would allow the skilled artisan to practice the full scope of the claimed invention, with the production of secondary treatment effects of conditions associated with human RhoB expression, and without undue experimentation. At the time of filing of the instant application there were no general guidelines for successful *in vivo* delivery of antisense compounds known in the art, nor are such guidelines provided in the specification as filed.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998: See IDS: AG), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Moreover, Crooke (1998), teach that there are a variety of factors that influence the behavior of an oligonucleotide in a cell. These factors include: oligonucleotide purity, oligonucleotide structure and modifications, structure of the RNA target in the cell, variations in cellular uptake and distribution, and binding to and effects of binding to non-nucleic acid targets, terminating mechanisms, misinterpretation of the effects of control oligonucleotides, the rates of synthesis and degradation of the target

mRNA and its protein, and the rates of metabolism of an oligonucleotide in cells (pages 3-7). Crooke clearly teaches that there is a significant level number of factors which influence the behavior of nucleic acid based compounds thereby rendering the activity of nucleic acid based therapeutics unpredictable, and thus much experimentation is required to screen multiple nucleic acid compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Branch (1998) also teach that "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of nucleic acid therapeutics to their specified target *in vivo* is unpredictable, the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Nucleic acid based therapy is a highly unpredictable field and the skill in the art is high.

Both Branch and Crooke teach that the behavior of nucleic acid based pharmaceuticals are unpredictable, therefore claims to nucleic acid based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the nucleic acid based therapy art.

Therefore, the specification as filed does not describe the *in vivo* method of inhibiting the expression of human RhoB, or the method of treating a human having a disease or condition associated with human RhoB by *in vivo* administration of antisense oligonucleotides targeting human RhoB mRNA, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the behavior of antisense compounds *in vivo* and further

with the production of the desired secondary effects, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining the structures of the small molecule inhibitors, and determining dosages and modes of delivery of the antisense oligonucleotides in a cell such that the expression of human RhoB is inhibited and the desired secondary effects are obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE